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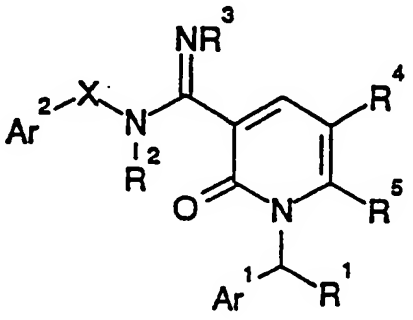

(I)

(57) Abstract

The invention relates to 2-pyridone derivatives of general formula (I) in which Ar^1 is an optionally substituted phenyl ring; Ar^2 is an optinally substituted phenyl ring; R^1 is hydrogen or C_{1-4}alkyl; R^2 is hydrogen or C_{1-4}alkyl; R^3 is hydrogen or C_{1-4}alkyl; R^4 and R^5 are the same or different and are each hydrogen, C_{1-4}alkyl or C_{1-4}alkylAr^1, or R^4 and R^5 together form a group $(CH=CH)_2$; and X is CH_2 or NR^6 in which R^6 is hydrogen or C_{1-4}alkyl or a salt thereof, and their use in therapy as gastric acid secretion inhibitors.

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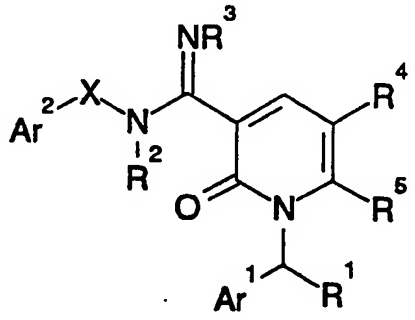
Pyridone derivatives, their preparation and use as medicines

The present invention relates to novel substituted pyridylamidine derivatives, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them, and their use in therapy, in particular as gastric acid secretion inhibitors.

The present invention, therefore, provides in a first aspect, compounds of structure (I):



(I)

in which

Ar^1 is an optionally substituted phenyl ring;

Ar^2 is an optionally substituted phenyl ring;

R^1 is hydrogen or C_{1-4}alkyl;

R^2 is hydrogen or C_{1-4}alkyl;

R^3 is hydrogen or C_{1-4}alkyl;

R^4 and R^5 are the same or different and are each hydrogen, C_{1-4}alkyl or C_{1-4}alkylAr^1, or R^4 and R^5 together form a group $(CH=CH)_2$; and

X is CH_2 or NR^6 in which R^6 is hydrogen or C_{1-4}alkyl

and salts thereof.

Suitably, Ar^1 is an optionally substituted phenyl ring. Suitable substituents for the phenyl ring Ar^1 include, for example, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, halogen, cyano, amino, C_{1-4}alkylamino, diC_{1-4}alkylamino, hydroxy, carbamoyl, carboxy, C_{1-6}alkanoyl trifluoromethyl, and C_{1-4}alkylenedioxy substituents such as methylenedioxy ($-OCH_2O-$). The phenyl ring may be substituted by a single

substituent, or by up to 5 substituents such as may be synthetically accessible. Preferably, the group Ar^1 is unsubstituted phenyl or phenyl substituted by 1 to 3 substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, halogen, cyano, amino, hydroxy, carbamoyl, carboxy, C_{1-6}alkanoyl or trifluoromethyl. More preferably Ar^1 is unsubstituted phenyl, or phenyl substituted by a single substituent selected from C_{1-6}alkyl, C_{1-6}alkoxy or halogen.

Suitably, Ar^2 is an optionally substituted phenyl ring. Suitable substituents for the phenyl ring Ar^2 include, for example, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, halogen, cyano, amino, hydroxy, carbamoyl, carboxy, C_{1-6}alkanoyl trifluoromethyl, and C_{1-4}alkylenedioxy substituents such as methylenedioxy ($-OCH_2O-$). The phenyl ring may be substituted by a single substituent, or by up to 5 substituents such as may be synthetically accessible. Preferably, the group Ar^2 is unsubstituted phenyl or phenyl substituted by 1 to 3 substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, halogen, cyano, amino, hydroxy, carbamoyl, carboxy, C_{1-6}alkanoyl or trifluoromethyl. More preferably Ar^2 is unsubstituted phenyl, or phenyl substituted by a single substituent selected from C_{1-6}alkyl, C_{1-6}alkoxy or halogen.

Suitably, R^1 is hydrogen or C_{1-4}alkyl; preferably R^1 is hydrogen.

Suitably, R^2 is hydrogen or C_{1-4}alkyl; preferably R^2 is hydrogen.

Suitably, R^3 is hydrogen or C_{1-4}alkyl; preferably R^3 is hydrogen.

Suitably, R^4 and R^5 are the same or different and are each, hydrogen, C_{1-4}alkyl or C_{1-4}alkylAr^1, or R^4 and R^5

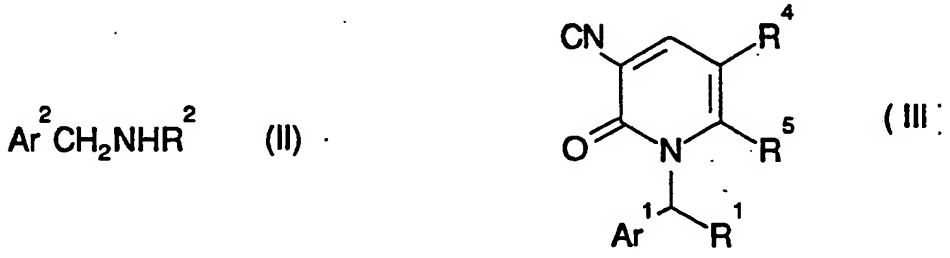
together form a $(CH=CH)_2$ group; preferably R^4 and R^5 are both hydrogen.

Suitably, X is CH_2 or NR^6; preferably X is CH_2 or NR^6 in which R^6 is C_{1-4}alkyl, in particular methyl.

Suitably R^6 is hydrogen or C_{1-4}alkyl; preferably R^6 is C_{1-4}alkyl.

The compounds of structure (I) and salts thereof can be prepared by procedures analogous to those known in the art. In a further aspect, there is therefore provided, a process for preparing compounds of structure (I) and salts thereof, which comprises:

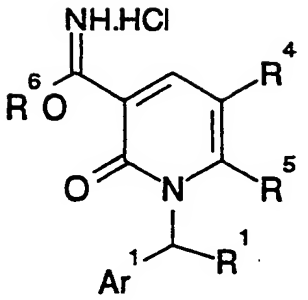
a) for compounds in which X is CH_2 and R^3 is hydrogen, reaction of a compound of structure (II) with a compound of structure (III):



(II) (III)

in which Ar^1, Ar^2, R^1, R^2, R^4 and R^5 are as described for structure (I); or

b) for compounds in which X is CH_2 and R^3 is hydrogen, reaction of a compound of structure (IV) with a compound of structure (II):



(IV)

in which
Ar^1 and R^1, R^4 and R^5 are as described for structure (I), and R^6 is C_{1-4}alkyl,
and optionally thereafter forming a salt thereof.

The reaction between compounds of structure (II) and compounds of structure (III) can be carried out in a suitable solvent such as ethanolic hydrochloric acid at ambient temperature or, more preferably, by first treating the compound of structure (II) with trimethylaluminium in a suitable solvent such as toluene or tetrahydrofuran and then adding the compound of structure (III) in a suitable solvent such as tetrahydrofuran to the reaction mixture, and heating at elevated temperature until the reaction is complete.

The reaction between compounds of structure (IV) and structure (II) can be carried out in a suitable solvent, such as, for example, dichloromethane, at ambient temperature, for as long as is necessary until the reaction is complete.

The intermediates of structures (II), (III) and (IV) are commercially available or can be prepared by standard techniques as hereinafter described.

The compounds of structure (I) and their pharmaceutically acceptable salts exert an anti-secretory effect by inhibition of the gastrointestinal H^+K^+ATPase enzyme (Fellenius, E., Berglindh, T., Sachs, G., Olke, L., Elander, B., Sjostrand, S.E., and Wallmark, B., 1981,

Nature, 290, 159-61).

In a further aspect therefore the present invention provides compounds of structure (I) and pharmaceutically acceptable salts thereof for use in therapy. The compounds of structure (I) and their pharmaceutically acceptable salts inhibit exogenously and endogenously stimulated gastric acid secretion and are useful in the treatment of gastrointestinal diseases in mammals, in particular humans. Such diseases include, for example, gastric and duodenal ulcers, aspiration pneumonitis and Zollinger-Ellison Syndrome.

Further, the compounds of structure (I) can be used in the treatment of other disorders where an anti-secretory effect is desirable for example in patients with gastritis, NSAID induced gastritis, acute upper intestinal bleeding, in patients with a history of chronic and excessive alcohol consumption, and in patients with gastro oesophageal reflux disease (GERD).

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of structure (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example,

ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains suitably from 1 to 1000 mg, preferably from 1 to 500 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The present invention also provides a method of inhibiting gastric acid secretion which comprises administering to a mammal in need thereof an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof; and a method of treatment of diseases of the stomach or intestine based on increased acid secretion which comprises administering to a mammal in need thereof an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

The pharmaceutically acceptable compounds of the invention will normally be administered to a subject for the treatment of gastrointestinal diseases and other conditions caused or exacerbated by gastric acidity. The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1 mg and 500 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

In addition, the compounds of the present invention can be co-administered with further active ingredients, such as antacids (for example magnesium carbonate or hydroxide and aluminium hydroxide), non-steroidal anti-flammatory drugs (for example indomethacin, aspirin or naproxen), steroids,

or nitrite scavengers (for example ascorbic acid or aminosulphonic acid), or other drugs used for treating gastric ulcers (for example histamine H_2-antagonists such as cimetidine), or agents capable of inhibiting the Helicobacter pylori organisms, for example antibiotics such as amoxicillin.

The following examples illustrate the invention. Temperatures are recorded in degrees centigrade.

Example 1

1-Benzyl-3-(N-benzylamidino)-2-pyridone hydrochloride

A) 1-Benzyl-3-cyano-2-pyridone

Petrol-washed sodium hydride (1.92 g, 80 mmol) was suspended in dry DMF (200 ml), 3-cyano-2-pyridone (9.0 g, 75 mmol) added portionwise, and the mixture stirred until evolution of hydrogen ceased. Benzyl bromide (13.7 g, 80 mmol) was then added slowly, keeping the temperature below 30°C. The mixture was stirred for a further 5 hours, then poured onto ice-water. The precipitate formed was filtered off and dried to give 1-benzyl-3-cyano-2-pyridone (11.68 g, 72%), m.p. 120-121°C.

B) 1-Benzyl-3-(N-benzylamidino)-2-pyridone hydrochloride

1-Benzyl-3-cyano-2-pyridone (6.0 g, 28.8 mmol) was dissolved in ethanolic HCl (250 ml) and allowed to stand at room temperature for 1 week. The solvent was evaporated and the residue dissolved in dry dichloromethane, cooled in ice, and a solution of benzylamine (50 ml, excess) in dichloromethane added slowly. Cooling was removed and the mixture stirred 2 hours at room temperature, then washed with water and aqueous bicarbonate, dried, and the solvent evaporated. Chromatography (silica gel, 4% methanol in chloroform), conversion to the hydrochloride and crystallisation from ethanol-ether gave the product (0.45 g), m.p. 186-188°C.

$C_{20}H_{19}N_3O \cdot HCl$

Found	C 68.05, H 5.71, N 11.81
Requires	C 67.90, H 5.70, N 11.90

Example 2

1-(4-Chlorobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

A) Preparation of 1-(4-chlorobenzyl)-3-cyano-2-pyridone

Substituting 4-chlorobenzyl chloride (6.44 g, 0.04 mol) for benzyl bromide and using corresponding molar proportions of the other reagents in example 1A gave 1-(4-chlorobenzyl)-3-cyano-2-pyridone (8.06 g, 82%), m.p. 139-140°C.

B) Preparation of 1-(4-chlorobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

To a stirred suspension of benzylamine hydrochloride in dry toluene (10 ml) at 5°C under nitrogen, was added dropwise a solution of 2M trimethylaluminium in toluene (6 ml, 0.012 mol) such that the temperature did not exceed 5°C . The mixture was allowed to reach room temperature and treated with 1-(4-chlorobenzyl)-3-cyano-2-pyridone (1 g, 0.004 mol) in tetrahydrofuran (20 ml) and left for 3 hours at 65°C. After cooling, the supernatant was decanted off and the residue treated with chloroform. The resulting solid was dissolved in a methanol/silica slurry, the suspension filtered, evaporated, and the residue triturated with ethanol. The resulting solid on recrystallisation from ethanol/ether gave 1-(4-chlorobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride (0.15 g, 10.5%), m.p. 207-209°C.

$C_{20}H_{18}N_3Cl \cdot HCl$

Found	C 61.93, H 4.95, N 11.16, Cl 18.18
Requires	C 61.86, H 4.93, N 10.82, Cl 18.26

Example 3

1-(2-Methylbenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

A) Preparation of 1-(2-methylbenzyl)-3-cyano-2-pyridone

Substituting 2-methylbenzyl bromide (7.4g ,0.04 mol) for benzyl bromide and using corresponding molar proportions of the other reagents in example 1A gave 1-(2-methylbenzyl)-3-cyano-2-pyridone (6.45g ,73%), m.p. 140-141°C.

B) Preparation of 1-(2-methylbenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

Benzylamine hydrochloride (1.06 g, 0.006 mol) was suspended in dry toluene to which 2M trimethylaluminium in toluene (2.9 ml, 0.006 mol) was added dropwise at 5°C under nitrogen. After allowing to reach 50°C, the mixture was treated with 1-(2-methylbenzyl)-3-cyano-2-pyridone (1.35 g, 0.006 mol) in dry tetrahydrofuran (20 ml) and left for 16 hours. After cooling, the mixture was poured onto a chloroform/silica slurry, washed with chloroform and then methanol. The methanol wash was evaporated and the residue partitioned between 2N NaOH/chloroform. The organic layer was separated, evaporated and distilled at 100°C (0.02 mm Hg). The residue was triturated with ethanol, causing crystallisation of unreacted cyanopyridone, which was filtered off. The filtrate was treated with ethanolic HCl to form crystals of 1-(2-methylbenzyl)-3-(benzylamidino)-2-pyridone hydrochloride (0.65 g, 29%), m.p. 230-231°C.

$C_{21}H_{21}N_3O \cdot HCl$

Found	C 68.63, H 6.09, N 11.73, Cl 9.62
Requires	C 68.56, H 6.03, N 11.42, Cl 9.64

Example 4
1-(4-Fluorobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

A) Preparation of 1-(4-fluorobenzyl)-3-cyano-2-pyridone

Substituting 4-fluorobenzyl chloride (5 g, 0.04 mol) for benzyl bromide and using corresponding molar proportions of the other reagents in example 1A gave 1-(4-fluorobenzyl)-3-cyano-2-pyridone (2.38 g, 26%), m.p. 118-120°C.

B) Preparation of 1-(4-fluorobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

Substituting 1-(4-fluorobenzyl)-3-cyano-2-pyridone (1.36 g, 0.006 mol) for 1-(2-methylbenzyl)-3-cyano-2-pyridone and using the corresponding molar proportions of the other reagents in example 3B gave 1-(4-fluorobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride (0.83 g, 35%) from ethanolic hydrogen chloride/ether, m.p. 186-187°C.

$C_{20}H_{18}FN_3O \cdot HCl$

Found	C 64.29, H 5.33, N 11.41, Cl 9.53
Requires	C 64.60, H 5.15, N 11.30, Cl 9.53

Example 5
1-(4-Nitrobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

A) Preparation of 1-(4-nitrobenzyl)-3-cyano-2-pyridone

Substituting 4-nitrobenzyl bromide (10 g, 0.08 mol) for benzyl bromide and using corresponding molar proportions of the other reagents in example 1A gave 1-(4-nitrobenzyl)-3-cyano-2-pyridone (18.98 g, 93%), m.p. 148-150°C.

B) Preparation of 1-(4-nitrobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

Substituting 1-(4-nitrobenzyl)-3-cyano-2-pyridone (1 g, 0.004 mol) for 1-(4-chlorobenzyl)-3-cyano-2-pyridone and using corresponding molar proportions of the other reagents in example 2B gave 1-(4-nitrobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride (0.15 g, 10%), m.p. 188-190°C.

$C_{20}H_{18}N_4O_3 \cdot HCl \cdot 0.2H_2O$

Found	C 59.50, H 4.76, N 13.76, Cl 8.82
Requires	C 59.59, H 4.86, N 13.90, Cl 8.84

Example 6

1-(4-Methoxybenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

A) Preparation of 1-(4-methoxybenzyl)-3-cyano-2-pyridone

Substituting 4-methoxybenzyl chloride (3.13 g, 0.02 mol) for benzyl bromide and using corresponding molar proportions of the other reagents in example 1A gave 1-(4-methoxybenzyl)-3-cyano-2-pyridone (1.49 g, 31%), m.p. 132-133°C.

B) Preparation of 1-(4-methoxybenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

Substituting 1-(4-methoxybenzyl)-3-cyano-2-pyridone (1.49 g, 0.006 mol) for 1-(4-chlorobenzyl)-3-cyano-2-pyridone and using corresponding molar proportions of the other reagents in example 2B gave 1-(4-methoxybenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride (0.24 g, 10%), m.p. 218-220°C

$C_{21}H_{21}N_3O_2 \cdot HCl$

Found	C 65.33, H 5.76, N 10.83, Cl 9.16
Requires	C 65.71, H 5.78, N 10.95, Cl 9.24

Example 7
1-(4-Benzyloxybenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

A) Preparation of 4-(benzyloxybenzyl)-3-cyano-2-pyridone

Substituting 4-benzyloxybenzyl chloride (5 g, 0.02 mol) for benzyl bromide and using corresponding molar proportions of the other reagents in example 1A gave 1-(4-benzyloxybenzyl)-3-cyano-2-pyridone (6.56 g, 93%), m.p. 109-110°C.

B) Preparation of 1-(4-benzyloxybenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

Substituting 1-(4-benzyloxybenzyl)-3-cyano-2-pyridone (4.74 g, 0.015 mol) for 1-(2-methylbenzyl)-3-cyano-2-pyridone and using corresponding molar proportions of the other reagents in example 3B gave 1-(4-benzyloxybenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride (1.22 g, 17%) from ethanolic hydrogen chloride/ether, m.p. 208-209°C.

$C_{27}H_{25}N_3O_2 \cdot HCl$

Found	C 70.50, H 5.70, N 9.14 , Cl 7.71
Requires	C 70.32, H 5.75, N 9.08 , Cl 7.78

Example 8
1-(2,6-Dichlorobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

A) Preparation of 1-(2,6-dichlorobenzyl)-3-cyano-2-pyridone

Substituting 2,6-dichlorobenzyl bromide for benzyl bromide (5 g, 0.04 mol) and using corresponding molar proportions of the other reagents in example 1A gave 1-(2,6-dichlorobenzyl)-3-cyano-2-pyridone (5.0 g, 44%), m.p. 181-182°C.

B) Preparation of 1-(2,6-dichlorobenzyl)-3-(N-benzyl-amidino)-2-pyridone hydrochloride

Substituting 1-(2,6-dichlorobenzyl)-3-(N-benzylamidino)-2-pyridone (1.67 g, 0.006 mol) for 1-(2-methylbenzyl)-3-cyano-2-pyridone and using corresponding molar proportions of the other reagents in example 3B gave 1-(2,6-dichlorobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride (0.09 g, 4%) from ethanolic hydrogen chloride/ether, m.p. 179-180°C.

$C_{20}H_{17}N_3Cl_2O \cdot 1.2HCl \cdot 0.17H_2O$

Found	C 55.22, H 4.10, N 9.48, Cl 25.80
Requires	C 55.47, H 4.31, N 9.70, Cl 26.19

Example 9

1-(2-Methylbenzyl)-3-(N-(2-methylbenzyl)amidino)-2-pyridone hydrochloride

Substituting 2-methylbenzylamine hydrochloride (0.95 g, 0.006 mol) for benzylamine hydrochloride and using corresponding molar proportions of the other reagents in example 3B gave 1-(2-methylbenzyl)-3-(N-(2-methylbenzyl)-amidino)-2-pyridone hydrochloride (0.33 g, 14%) from ethanolic hydrogen chloride/ether, m.p. 212-213°C.

$C_{22}H_{23}N_3O \cdot HCl$

Found	C 68.75, H 6.42, N 10.95, Cl 9.23
Requires	C 69.19, H 6.33, N 11.00, Cl 9.28

Example 10

1-Benzyl-3-(N-(4-fluorobenzyl)amidino)-2-pyridone hydrochloride

4-Fluorobenzylamine hydrochloride (1.37 g, 0.0085 mol) was suspended in dry toluene to which 2M trimethylaluminium in toluene (4.5 ml, 0.0085 mol) was added dropwise at 5°C under nitrogen. After allowing to reach 50°C, the mixture was treated with 1-benzyl-3-cyano-2-pyridone (1.8 g, 0.0085 mol) in dry tetrahydrofuran (20 ml) and left for 16 hours. After cooling, the mixture was poured onto a chloroform/silica

slurry, washed with chloroform and then methanol. The methanol wash was evaporated and the residue partitioned between 2N NaOH and chloroform. The organic layer was separated, evaporated and distilled at 100°C (0.02 mm Hg). The residue was triturated with ethanol causing crystallisation of unreacted cyanopyridone, which was filtered off. The filtrate was treated with ethanolic hydrogen chloride to form crystals of 1-benzyl-3-(N-(4-fluorobenzyl)amidino)-2-pyridone hydrochloride (0.33 g, 10%), m.p. 199-200°C.

	$C_{20}H_{10}FN_3O \cdot HCl$
Found	C 64.65, H 5.19, N 11.38, Cl 9.53
Requires	C 64.60, H 5.15, N 11.30, Cl 9.53

Example 11

1-Benzyl-3-(N-(2-methylbenzyl)amidino)-2-pyridone hydrochloride

Substituting 2-methylbenzylamine hydrochloride (1.34 g, 0.0085 mol) for 4-fluorobenzylamine hydrochloride and using corresponding molar proportions of the other reagents in example 10 gave 1-benzyl-3-(N-(2-methybenzyl)amidino)-2-pyridone hydrochloride (0.47 g, 15%) from ethanolic hydrogen chloride/ether, m.p. 155-156°C.

	$C_{21}H_{21}N_3O \cdot 1.15HCl$
Found	C 67.26, H 5.98, N 11.30, Cl 10.53
Requires	C 67.56, H 5.98, N 11.26, Cl 10.92

Example 12

1-(4-Methoxybenzyl)-3-(N-(2-methylbenzyl)amidino)-2-pyridone hydrochloride

Substituting 1-(4-methoxybenzyl)-3-cyano-2-pyridone (2.8 g, 0.012 mol) for 1-benzyl-3-cyano-2-pyridone and using corresponding molar proportions of the other reagents in example 11 gave 1-(4-methoxybenzyl)-3-(N-(2-methylbenzyl)-amidino)-2-pyridone hydrochloride (0.28 g, 6%) from ethanolic hydrogen chloride/ether, m.p. 182-183°C.

	$C_{22}H_{23}N_3O \cdot HCl$
Found	C 66.29, H 6.08, N 10.54, Cl 9.03
Requires	C 66.41, H 6.08, N 10.56, Cl 8.91

Example 13

1-Benzyl-3-(N-(4-chlorobenzyl)amidino)-2-pyridone hydrochloride

4-Chlorobenzylamine hydrochloride (2.5 g, 0.014 mol) was suspended in dry toluene to which 2M trimethylaluminium in toluene (7 ml, 0.014 mol) was added dropwise at 5°C under nitrogen. After allowing to reach 50°C, the mixture was treated with 1-benzyl-3-cyano-2-pyridone (1 g, 0.0047 mol) in dry tetrahydrofuran (20 ml) and left for 16 hours. After cooling, the supernatent was decanted off and the residue treated with chloroform. This caused formation of a solid which was dissolved in a methanol/silica slurry. The suspension was filtered, evaporated and triturated with ethanol, causing crystallization of 1-benzyl-(N-(4-chlorobenzyl)amidino)-2-pyridone hydrochloride (0.15 g, 10.5%), m.p. 207-209°C.

	$C_{20}H_{18}N_3ClO \cdot HCl$
Found	C 61.46, H 4.85, N 10.83, Cl 18.57
Requires	C 61.87, H 4.93, N 10.82, Cl 18.26

Example 14

1-Benzyl-3-(N-(4-trifluoromethylbenzyl)amidino)-2-pyridone hydrochloride

Substituting 4-trifluoromethylbenzylamine hydrochloride (1.26 g, 0.06 mol) for 4-fluorobenzylamine hydrochloride and using corresponding molar proportions of the other reagents in example 10 gave 1-benzyl-3-(N-(4-trifluoromethylbenzyl)amidino)-2-pyridone hydrochloride (0.32 g, 13%) from ethanolic hydrogen chloride/ether, m.p. 179-180°C.

$C_{21}H_{18}N_3F_3O \cdot HCl$

Found	C 59.42, H 4.68, N 9.72, Cl 8.41
Requires	C 59.79, H 4.54, N 9.96, Cl 8.40

Example 15

1-Benzyl-3-(N-(4-methoxybenzyl)amidino)-2-pyridone hydrochloride

Substituting 4-methoxybenzylamine hydrochloride (1.47 g, 0.0085 mol) for 4-fluorobenzylamine hydrochloride and using corresponding molar proportions of the other reagents in example 10 gave 1-benzyl-3-(N-(4-methoxybenzyl)amidino)-2-pyridone hydrochloride (0.31 g, 9.5%) from ethanolic hydrogen chloride/ether, m.p. 175-176°C.

$C_{21}H_{21}N_3O_2 \cdot HCl$

Found	C 65.51, H 5.84, N 11.02, Cl 9.18
Requires	C 65.71, H 5.78, N 10.95, Cl 9.24

Example 16

1-Benzyl-3-(N-(4-methylbenzyl)amidino)-2-pyridone hydrochloride

Substituting 4-methylbenzylamine hydrochloride (0.95 g, 0.006 mol) for 4-fluorobenzylamine hydrochloride and using corresponding molar proportions of the other reagents in example 10 gave 1-benzyl-3-(N-(4-methylbenzyl)amidino)-2-pyridone hydrochloride (0.16 g, 7%) from ethanolic hydrogen chloride/ether, m.p. 193-194°C.

$C_{21}H_{21}N_3O \cdot HCl$

Found	C 68.26, H 6.03, N 11.39, Cl 9.77
Requires	C 68.56, H 6.03, N 11.42, Cl 9.64

Example 17

1-(4-Methylbenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

A) 1-(4-Methylbenzyl)-3-cyano-2-pyridone

Substituting 4-methylbenzyl bromide (7.4 g, 0.04 mol) for benzyl bromide and using corresponding molar proportions of the other reagents in example 1A gave 1-(4-methylbenzyl)-3-cyano-2-pyridone (6.67 g, 73%), m.p. 144-145°C.

B) 1-(4-Methylbenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride

Benzylamine hydrochloride (1.06 g, 0.006 mol) was suspended in dry tetrahydrofuran (20 ml), to which 2M trimethylaluminium in toluene (2.9 ml, 0.006 mol) was added dropwise at 5°C under nitrogen. The mixture was warmed to 50 °C, then treated with 1-(4-methylbenzyl)-3-cyano-2-pyridone (1.35 g, 0.006 mol) in dry tetrahydrofuran (20 ml) and left for 16 hours. After cooling, the mixture was poured onto a chloroform/silica slurry, washed with chloroform and then methanol. The methanol wash was evaporated and the residue partitioned between 2N NaOH and chloroform. The organic layer was separated, evaporated and distilled at 100°C (0.002 mm Hg). The residue was treated with ethanolic hydrogen chloride to form crystals of 1-(4-methylbenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride (0.73 g, 33%), m.p. 209-210°C.

$C_{21}H_{21}N_3O \cdot 1.0HCl$

Found	C 68.08, H 6.00, N 11.39, Cl 9.91
Requires	C 68.56, H 6.03, N 11.42, Cl 9.64

Example 18

1-(4-Dimethylaminobenzyl)-3-(N-benzylamidino)-2-pyridone dihydrochloride

A) 1-(4-Dimethylaminobenzyl)-3-cyano-2-pyridone

Substituting 4-dimethylaminobenzyl chloride (8.5 g, 0.04 mol) for benzyl bromide and using corresponding molar proportions of the other reagents in example 1A gave 1-(4-dimethylamino)-3-cyano-2-pyridone (0.65 g, 6.4%), m.p. 153-155°C.

B) 1-(4-Dimethylaminobenzyl)-3-(N-benzylamidino)-2-pyridone dihydrochloride

Substituting 4-(dimethylaminobenzyl)-3-cyano-2-pyridone (1.37 g, 0.005 mol) for 1-benzyl-3-cyano-2-pyridone and using corresponding molar proportions of the other reagents in example 11 gave 1-(4-dimethylaminobenzyl)-3-(N-benzylamidino)-2-pyridone dihydrochloride (0.2 g, 9.2%), m.p. 210-211°C.

$C_{22}H_{24}N_4O \cdot 2HCl$

Found	C 60.17, H 6.10, N 12.64, Cl 15.83
Requires	C 60.11, H 6.13, N 12.75, Cl 16.04

Example 19

1-(4-Methoxybenzyl)-3-(N-(2-methylbenzyl)amidino)-2-quinolone hydrochloride

A) 1-(4-Methoxybenzyl)-3-cyano-2-quinolone

To a solution of sodium ethoxide (made from 0.81g of sodium and ethanol) in ethanol (200 ml) was added 3-cyano-2-quinolone (6 g, 0.035 mol) and the mixture stirred overnight at room temperature. The reaction mixture was poured into diethyl ether (200 ml) and the solid obtained was collected by filtration and air dried. To a slurry of the sodium salt in dimethylformamide (50 ml) was added 4-methoxybenzyl chloride (5 ml, 0.037 mol) and the reaction mixture stirred at room temperature overnight. The reaction mixture was poured onto ice/water and the solid obtained was collected by filtration and dried. The solid was purified by flash chromatography using chloroform as eluant. The fractions containing the pure product were combined and evaporated under reduced pressure to give the title compound (4.5g, 44%), m.p. 178-180°C.

B) 1-(4-Methoxybenzyl)-3-(N-(2-methylbenzyl)amidino)-2-quinolone hydrochloride.

Substituting 1-(4-methoxybenzyl)-3-cyano-2-quinolone (2 g, 0.0069 mol) for 1-(2-methylbenzyl)-3-cyano-2-pyridone and using corresponding molar proportions of the other reagents in example 3B gave the title compound (0.12 g, 4.2%). m.p. >250°C.

$C_{26}H_{25}N_3O_2 \cdot HCl$

Found	C 69.80, H 5.91, N 9.46, Cl^- 7.81
Requires	C 69.71, H 5.85, N 9.38, Cl^- 7.91

Example 20

1-Benzyl-3-(N-benzylamidino)-2-quinolone hydrochloride

A) 1-Benzyl-3-cyano-2-quinolone

To a slurry of sodium hydride (2 g, 0.05 mol) in dimethylformamide (50 ml) was added a slurry of 3-cyano-2-quinolone (8.5 g, 0.05 mol) in dimethylformamide (100 ml) dropwise. On completion of the addition the mixture was stirred for 30 minutes, then benzyl bromide (8.6 g, 0.05 mol) was added dropwise keeping the temperature below 20°C using an ice/salt bath. Stirring was continued at room temperature overnight, the mixture was poured onto ice/water (500 ml), and the solid obtained was collected by filtration and dried (8.5 g, 65%), m.p. 193-195°C.

B) 1-Benzyl-3-(N-benzylamidino)-2-quinolone hydrochloride

Substituting 1-benzyl-3-cyano-2-quinolone (2 g, 0.008 mol) for 1-(2-methylbenzyl)-3-cyano-2-pyridone and using corresponding molar proportions of the other reagents in example 3B gave 1-benzyl-3-(N-benzylamidino)-2-quinolone hydrochloride (0.25 g, 8.8%), m.p. >250°C

$C_{24}H_{20}N_3O \cdot HCl$

Found	C 71.28, H 5.56, N 10.41, Cl^- 8.59
Requires	C 71.55, H 5.25, N 10.43, Cl^- 8.80

Example 21

1-Benzyl-3-(N-benzylamidino)-6-methyl-2-pyridone hydrochloride

A) 1-Benzyl-3-cyano-6-methyl-2-pyridone

To a slurry of sodium hydride (6 g, 0.15 mol) in dimethylformamide (150 ml) was added 6-methyl-3-cyano-2-pyridone (20 g, 0.149 mol) portionwise. On completion of the addition the reaction mixture was stirred for 30 minutes, warming to 40°C to dissolve the pyridone, then cooled to below 20°C and benzyl bromide (17.2 ml, 0.145 mol) added dropwise. Stirring was continued overnight, the mixture was poured onto ice/water and extracted with diethyl ether (3x200 ml). The ether extracts were combined, dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography using chloroform as eluant. Fractions containing the product were combined and evaporated under reduced pressure to give an oil, which crystallized on addition of hexane. The solid was collected by filtration to give the title compound (13.8 g, 41%), m.p. 101-103°C.

B) 1-Benzyl-3-(N-benzylamidino)-6-methyl-2-pyridone hydrochloride

Substituting 1-benzyl-3-cyano-6-methyl-2-pyridone (2 g, 0.009 mol) for 1-(2-methylbenzyl)-3-cyano-2-pyridone and using corresponding molar proportions of the other reagents in example 3B gave the title compound (0.72 g, 22%), m.p. 183-185°C.

$C_{21}H_{29}N_3O \cdot HCl$

Found	C 68.35, H 5.98, N 11.49, Cl^- 9.47
Requires	C 68.56, H 6.03, N 11.42, Cl^- 9.64

Example 22

1-Benzyl-3-(N-(N-phenyl)amidino)-2-pyridone hydrochloride

A stirred solution of phenylhydrazine (1.5 g, 14 mmol) in dry THF (20 ml) was treated at 0°C with a 1.0M solution of dimethylaluminium chloride in hexane (14.4 ml. 14.4 mmol). When effervescence ceased, a solution of 1-benzyl-3-cyano-2-pyridone (1.0 g, 4.8 mmol) in dry THF (20 ml) was added and the mixture warmed to 40°C, then poured onto a silica gel/chloroform slurry. Non-polar materials were removed by washing the gel with chloroform. The product was eluted with methanol, which was evaporated and the residue recrystallised from an isopropyl alcohol/ether mixture to give the title compound as an orange/yellow solid (90 mg, 5%) m.p. 185-6°C.

$C_{19}H_{19}N_4O \cdot 1.3HCl$

Found	C 61.98, H 5.21, N 15.10
Requires	C 62.38, H 5.32, N 15.32

Example 23

1-Benzyl-3-(N-(N-methyl-N-phenyl)amidino)-2-pyridone hydrochloride

Substituting 1-methyl-1-phenylhydrazine hydrochloride (0.95g, 0.006 mol) for benzylamine hydrochloride and using corresponding molar proportions of the other reagents in example 3B gave 1-benzyl-3-(N-(N-methyl-N-phenyl)amidino)-2-pyridone hydrochloride (0.18g, 8%), m.p. 147-149°C.

$C_{20}H_{20}N_4O. 1. 0 HCl. 0.2 H_2O$

Found	C 64.51, H 5.70, N 15.22, Cl 9.41
Requires	C 64.49, H 5.79, N 15.04, Cl 9.51

Example 24

1-Benzyl-3-(N-benzylamidino)-5-methyl-2-pyridone hydrochloride

A) 1-Benzyl-3-cyano-5-methyl-2-pyridone

To a solution of sodium ethoxide (prepared from 1.37g of sodium and ethanol) in ethanol (200 ml) was added 3-cyano-5-methyl-2-pyridone (8.0g, 0.06 mol) and the mixture stirred overnight at room temperature. The reaction mixture was poured into ether (200 ml) and the solid obtained collected by filtration and air dried. A slurry of the sodium salt in dimethylformamide (100 ml) was treated with benzyl bromide (10.2g, 0.06 mol) and the reaction mixture stirred at room temperature overnight. The reaction was poured into ice/water and the solid collected by filtration, washed with a little ether and dried to give 1-benzyl-3-cyano-5-methyl-2-pyridone (11.75g, 88%), m.p. 179-182°C.

B) 1-Benzyl-3-(N-benzylamidino)-5-methyl-2-pyridone hydrochloride.

Substituting 1-benzyl-3-cyano-5-methyl-2-pyridone (2.0g, 0.009 mol) for 1-(2-methylbenzyl)-3-cyano-2-pyridone and using corresponding molar proportions of the other reagents in example 3B gave 1-benzyl-3-(N-benzylamidino)-5-methyl-2-pyridone hydrochloride (1.71g, 52%). m.p. 155-156°C.

$C_{21}H_{29}N_3O.HCl$

Found	C 67.97, H 6.00, N 11.21, Cl 9.48
Requires	C 68.56, H 6.03, N 11.42, Cl 9.64

Biological Data.

H^+K^+ATPase Activity.

The effects of a single high concentration (100 μM) of a compound of structure (I) on K-stimulated ATPase activity in lyophilised gastric vesicles was determined. Preferred compounds of structure (I) were also tested over a range of concentrations to determine IC_{50} values.

(i) **Preparation of lyophilised gastric vesicles (H/K-ATPase).**

Lyophilised gastric vesicles were prepared from pig fundic mucosa after the method of Keeling et. al. (Biochem. Pharmacol., 34, 2967, 1985).

(ii) **K^+-stimulated ATPase activity.**

K^+-stimulated ATPase activity was determined at 37°C in the presence of the following : 10 mM Pipes/Tris buffer pH 7.0, 2 mM $MgSO_4$, 1 mM KCl, 2 mM Na_2ATP and 3-6 μg protein/ml lyophilised gastric vesicles. After incubation for 30 minutes, the inorganic phosphate hydrolysed from ATP was determined by the method of Yoda and Hokin (Biochem. Biophys. Res. Commun. 40, 880, 1970).

Compounds of structure (I) were dissolved in dimethylsulphoxide which up to the highest concentration used had no effect on K^+-stimulated ATPase activity.

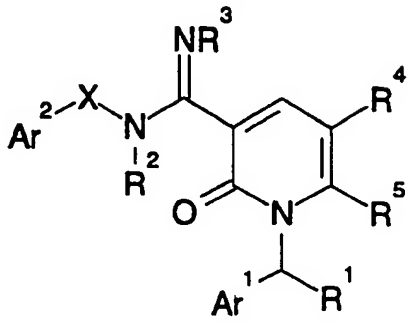
The effect of the highest concentration of each compound of structure (I) on the recovery of a standard amount of inorganic phosphate was also determined.

Results

The compounds of examples 1 to 23 had IC_{50} values of less than 20 µM.

Claims:

1. A compound of structure (I):



(I)

in which
Ar^1 is an optionally substituted phenyl ring;
Ar^2 is an optionally substituted phenyl ring;
R^1 is hydrogen or C_{1-4}alkyl;
R^2 is hydrogen or C_{1-4}alkyl;
R^3 is hydrogen or C_{1-4}alkyl;
R^4 and R^5 are the same or different and are each hydrogen, C_{1-4}alkyl or C_{1-4}alkylAr^1, or R^4 and R^5 together form a group $(CH=CH)_2$; and
X is CH_2 or NR^6 in which R^6 is hydrogen or C_{1-4}alkyl
or a salt thereof.

2. A compound according to claim 1 in which Ar^1 is phenyl, X is CH_2 and Ar^2 is phenyl.

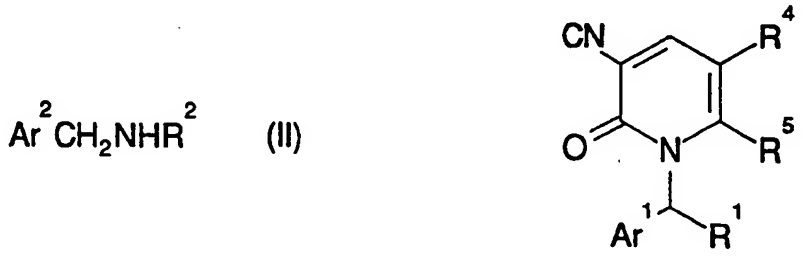
3. A compound according to claim 2 in which R^1 to R^3 are all hydrogen.

4. A compound according to claim 1 which is:
1-benzyl-3-(N-benzylamidino)-2-pyridone hydrochloride;
1-(4-chlorobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride;
1-(2-methylbenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride;
1-(4-fluorobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride;

1-(4-nitrobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride; 1-(4-methoxybenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride;
1-(4-benzyloxybenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride;
1-(2,6-dichlorobenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride;
1-(2-methylbenzyl)-3-(N-(2-methylbenzyl)amidino)-2-pyridone hydrochloride;
1-benzyl-3-(N-(4-fluorobenzyl)amidino)-2-pyridone hydrochloride;
1-benzyl-3-(N-(2-methylbenzyl)amidino)-2-pyridone hydrochloride;
1-(4-methoxybenzyl)-3-(N-(2-methylbenzyl)amidino)-2-pyridone hydrochloride;
1-benzyl-3-(N-(4-chlorobenzyl)amidino)-2-pyridone hydrochloride;
1-benzyl-3-(N-(4-trifluoromethylbenzyl)amidino)-2-pyridone hydrochloride;
1-benzyl-3-(N-(4-methoxybenzyl)amidino)-2-pyridone hydrochloride;
1-benzyl-3-(N-(4-methylbenzyl)amidino)-2-pyridone hydrochloride;
1-(4-methylbenzyl)-3-(N-benzylamidino)-2-pyridone hydrochloride;
1-(4-dimethylaminobenzyl)-3-(N-benzylamidino)-2-pyridone dihydrochloride;
1-(4-methoxybenzyl)-3-(N-(2-methylbenzyl)amidino)-2-quinolone hydrochloride;
1-benzyl-3-(N-benzylamidino)-2-quinolone hydrochloride;
1-benzyl-3-(N-benzylamidino)-6-methyl-2-pyridone hydrochloride;
1-benzyl-3-(N-(N-phenyl)amidino)-2-pyridone hydrochloride;
1-benzyl-3-(N-(N-methyl-N-phenyl)amidino)-2-pyridone hydrochloride; or
1-benzyl-3-(N-benzylamidino)-5-methyl-2-pyridone hydrochloride.

5. A process for preparing a compound according to claim 1 which comprises:

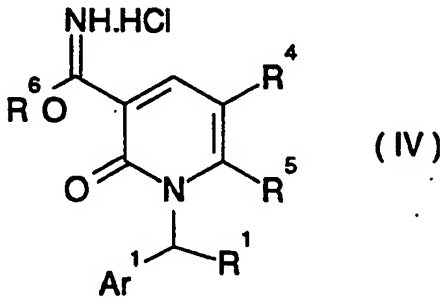
a) for compounds in which X is CH_2 and R^3 is hydrogen, reaction of a compound of structure (II) with a compound of structure (III):



(II) (III)

in which Ar^1, Ar^2, R^1, R^2, R^4 and R^5 are as described for structure (I); or

b) for compounds in which X is CH_2 and R^3 is hydrogen, reaction of a compound of structure (IV) with a compound of structure (II):



(IV)

in which
Ar^1 and R^1, R^4 and R^5 are as described for structure (I), and R^6 is C_{1-4}alkyl.

6. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

7. A compound according to any one of claims 1 to 4 for use in therapy, in particular as gastric acid secretion inhibitors.

8. A compound of structure (III) as described in claim 5.

9. A compound of structure (IV) as described in claim 5.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/00175

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D213/78; C07D215/54; A61K31/44; A61K31/47

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	US,A,3 299 081 (MERCK & CO., INC.) 17 January 1967 see the whole document ---	5
A	EP,A,0 339 768 (SMITHKLINE BECKMAN INTERCREDIT B.V.) 2 November 1989 see claims 1,4-6; examples ---	1,6,7
A	US,A,4 284 768 (A.A. SANTILLI) 18 August 1981 see the whole document ---	1,6,7
X,P	EP,A,0 500 297 (FISONS PLC) 26 August 1992 see claim 1; examples 1-3 ---	8

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
07 APRIL 1993	29. 04. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P. BOSMA

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	US,A,4 028 084 (P.J. MCNULTY ET AL.) 7 June 1977 see example XIIIb	8
X	TETRAHEDRON, (INCL. TETRAHEDRON REPORTS) vol. 36, no. 6, 1980, OXFORD GB pages 785 - 789 F.M. MORACCI ET AL. 'Covalent adducts from 1,3-disubstituted pyridinium salts and pyridine' see compound 7b	8
X	CHEMICAL ABSTRACTS, vol. 95, no. 13, 28 September 1981, Columbus, Ohio, US; abstract no. 115245n, W.H. GUENDEL ET AL. 'Pseudobases from quinolinium salts and alkoxides.' page 675 ; see CAS RN 78860-04-5 & ZEITSCHRIFT FÜR NATURFORSCHUNG, TEIL B: ANORGANISCHE CHEMIE, ORGANISCHE CHEMIE. vol. 36B, no. 6, 1981, TÜBINGEN DE pages 745 - 749	8

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9300175
SA 70683

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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		JP-A- 1261374	18-10-89
		US-A- 5089498	18-02-92
US-A-4284768	18-08-81	None	
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		WO-A- 9214714	03-09-92
US-A-4028084	07-06-77	US-A- 4104273	01-08-78